Remarks

I. Status Of The Claims And Support For The Amendments

Claims 2-3, 5, 7, 9, 11-15, 17, 19-20, and 23-24 have been amended. Claim 1 has been canceled. Two new claims, Claims 40 and 41, have been added.

Support for the addition of Claim 40 is found in the Specification at page 20, paragraphs [0073] and [0076]; page 23, paragraphs [0085] to [0087]; page 31to page 32, paragraphs [0115]- [0121]); page 34, paragraph [0131]; Figure 6; page 38, paragraphs [0147] and [0148]; and original Claim 10. Support for the addition of Claim 41 is found in the Specification at pages 24-25, paragraphs [0091]-[0092].

No new matter has been added by these amendments.

Based on the above amendments and the following remarks, Applicants respectfully request that the Examiner reconsider and withdraw all of the outstanding rejections.

II. The Rejection Under 35 U.S.C. § 112 Should Be Withdrawn

Claims 13 and 14 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite. Applicants respectfully traverse this rejection.

It is the Examiner's view that in Claims 13 and 14, the phrase "inlets that are situated close to each other" is vague and indefinite. It is also the Examiner's view that Claim 14 is indefinite because it is dependent on Claim 13. To expedite prosecution, and without acquiescing to the rejection, the phrase "inlets that are situated close to each other" has been deleted from Claim 13. Currently pending Claim 13 now precisely describes the invention and therefore renders the Examiner's rejection moot. Likewise,

Applicant's submit that Claim 14 which is dependent upon Claim 13 is no longer indefinite. Therefore, Applicants respectfully request that this rejection be reconsidered and withdrawn.

III. The Rejections Under 35 U.S.C. § 103(a) Should Be Withdrawn

A. The Rejection Over QIAGEN In View Of Santoro Should Be Withdrawn

Claims 1-2, 5, 7-9, 12, 15, 17 and 19-20 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over QIAGEN in view of Santoro *et al.*, U.S. Patent No. 6,660,472 ("Santoro"). Applicants respectfully traverse this rejection.

QIAGEN discloses a manual method of producing plasmid DNA wherein an alkaline lysis step is followed by a clarification and purification step. However, as the Examiner acknowledges:

> QIAGEN does not teach that process comprising the step of disintegrating cells by alkaline lysis by contacting the cell suspension with an alkaline lysis solution and allowing the cell suspension and the alkaline lysis solution to flow through a lysis reactor that is filled with particulate material.

See Office Action p. 7.

The Examiner asserts that Santoro discloses method of lysing bacterial cells releasing nucleic acid released by a lysis step in the presence of particulate beads, such as glass beads. The Examiner also asserts that Santoro's disclosure would provide motivation for one skilled in the art to combine Santoro with QIAGEN to produce biomolecules, such as plasmid DNA. However, Applicants respectfully disagree.

The disclosure of Santoro is incompatible with the *alkaline lysis* method of QIAGEN. Santoro *mechanically* lyses bacterial cells to release nucleic acids by vortexing the bacterial cells in a tube containing particulate material, such as glass beads. *Mechanically lysing* bacterial cells according to the method of Santoro will shear the genomic DNA present in the bacterial cells, thereby contaminating the biomolecule of interest with bacterial genomic DNA. In this regard, combining Santoro with QIAGEN, does not arrive at the presently claimed invention, which avoids mechanical shearing.

Even assuming, *arguendo*, that Santoro can be combined with QIAGEN, Santoro fails to suggest that the manual method for purifying nucleic acid in QIAGEN could be altered such that the lysis, neutralization and clarification reactors are fluidly connected. The claimed method requires that the reactors be fluidly connected, thereby reducing the likelihood of contaminating the biomolecule of interest with environmental contaminants, such as pathogens. Therefore, the products produced according the presently claimed method are superior in purity compared to the products produced by the methods of either QIAGEN or Santoro.

Furthermore, the requirement of the claims that the reactors be fluidly connected, is not simply a structural element that has no impact on the quality of the biomolecule produced. Fluidly connecting the reactors produces an essentially closed system, thereby preventing potential environmental contamination. Nothing in the disclosure of either QIAGEN or Santoro would suggest an automated or semi-automated method that incorporates fluidly connecting three distinct reactors to produce a biomolecule of interest.

In addition, Santoro fails to suggest that the manual method for purifying nucleic acid in QIAGEN could be scaled to a manufacturing level. The presently claimed invention specifies that the biomolecule be produced on a manufacturing scale.

> The process of the invention is scalable for processing large amounts of polynucleotide containing cells, it may be operated on a "manufacturing scale", to typically process more than 100 grams wet cells, and yielding amounts from 0.1 g to 100 g up to kg of the polynucleotide of interest that meet the demands of clinical trials as well as for market supply.

See page 31, paragraph [0115].

The QIAGEN method produces approximately 500 μg of plasmid DNA which is a typical laboratory production scale. Santoro does not cure the deficiency of QIAGEN. Santoro simply discloses the advantage of using beads to *mechanically lyse* cells and extract nucleic acid on a laboratory scale similar to QIAGEN, but does not disclose the production of highly purified biomolecules on a manufacturing scale as in the presently claimed invention.

The method of the presently claimed invention offers the advantage of increased productivity and convenience over known methods of producing biomolecules, such as plasmid DNA. Santoro fails to suggest that the manual method for purifying nucleic acid in QIAGEN could increase productivity and convenience while reducing the variability between samples. In addition, the method of the presently claimed invention offers the advantage of reducing batch-to-batch variability that would naturally occur while following the manual methods of taught by either QIAGEN or Santoro. Based on the amendment to the claims and the arguments presented above, Applicants respectfully request that this rejection be reconsidered and withdrawn.

B. The Rejection Over QIAGEN In View Of Santoro and Further in View of Craig Should Be Withdrawn

Claims 24 stands rejected under 35 U.S.C. § 103 as allegedly obvious over QIAGEN in view of Santoro et al., U.S. Patent No. 6,660,472 ("Santoro") and further in view of Craig, U.S. Patent No. 6,381,967 ("Craig"). Applicants respectfully traverse this rejection.

Craig fails to suggest that the manual method for purifying nucleic acid in QIAGEN or Santoro be altered such that the three reactors are fluidly connected, so that the lysed cell solution is fluidly connected to the neutralization reactor and the neutralization reactor is fluidly connected to the clarification reactor. Moreover, Craig fails to suggest that the manual method of QIAGEN or Santoro be modified such that the biomolecules are produced on a manufacturing scale.

The incompatibilities of QIAGEN and Santoro are discussed above. However, even in combination, QIAGEN, Santoro and Craig do not have suggest the method of Claim 24. While Craig discloses a method of cryopreservation that functions to store biomolecules of interest in intact cells for extended periods this is only one element of the overall method of the presently claimed invention. As Craig fails to remedy the deficiencies of QIAGEN and Santoro, Applicants respectfully request that this rejection be reconsidered and withdrawn.

C. The Rejection Over Gonzales In View Of Santoro Should Be Withdrawn

Claims 1-5, 9, 15, 19-20 and 23 stand rejected under 35 U.S.C. § 103 as allegedly obvious over Gonzales, U.S. Patent No. 5,783,686 ("Gonzales") in view of Santoro et al., U.S. Patent No. 6,660,472 ("Santoro"). Applicants respectfully traverse this rejection.

The mechanical lysis method of Santoro is incompatible with the alkaline lysis method of Gonzales. The mechanical lysis method of Santoro uses particulate matter, such as glass beads, in conjunction with vortexing to *mechanically lyse* bacterial cells. The automated *alkaline lysis* method of Gonzales, emphasizes the gentle handling of the lysate to avoid shearing and subsequent contamination of the plasmid DNA with genomic DNA. Therfore, the method of Santoro is incompatible with, not combineable with, and teaches away from the method of Gonzales and the presently claimed invention.

Even assuming, *arguendo*, that Santoro does not teach away from the disclosure of Gonzales and the presently claimed invention, Santoro fails to suggest that the automated method for purifying nucleic acid in Gonzales could be altered such that the lysis, neutralization and clarification reactors are fluidly connected, so that the lysed cell solution is fluidly connected to the neutralization reactor and the neutralization reactor is fluidly connected to the clarification reactor.

Moreover, there is no teaching or suggestion that the automated method of Gonzales could be modified such that biomolecules are produced on a manufacturing scale. Gonzales discloses an automated liquid handling station that utilizes an alkaline lysis protocol to produce numerous small scale samples of plasmid DNA, primarily for automated sequencing. While this disclosure is advantageous for producing numerous

small scale samples of plasmid DNA, nothing in the disclosure of Santoro would lead a person of skill in the art to arrive at the presently claimed invention of producing biomolecules, such as plasmid DNA, on a manufacturing scale. Since, Santoro fails to make up for many of the deficiencies of Gonzales, Applicants respectfully request that this rejection be reconsidered and withdrawn.

C. The Rejection Over Gonzales In View of Santoro and Further in View of Craig Should Be Withdrawn

Claims 24 stands rejected under 35 U.S.C. § 103 as allegedly obvious over Gonzales, U.S. Patent No. 5,783,686 ("Gonzales") in view of Santoro et al., U.S. Patent No. 6,660,472 ("Santoro") and further in view of Craig, U.S. Patent No. 6,381,967 ("Craig"). Applicants respectfully traverse this rejection.

Craig fails to suggest that the automated alkaline lysis method for purifying nucleic acid as in Gonzales or the use of glass beads to mechanically lyse cells as in Santoro be altered such that the three reactors are fluidly connected, so that the lysed cell solution is fluidly connected to the neutralization reactor and the neutralization reactor is fluidly connected to the clarification reactor. Moreover, Craig fails to suggest that the automated alkaline lysis method of Gonzales or the manual mechanical lysis method of Santoro be modified such that the biomolecules are produced on a manufacturing scale.

The deficiencies of Gonzales and Santoro are discussed above. However, even in combination, Gonzales, Santoro and Craig do not provide all of the elements of the method of Claims 24 which is currently dependent upon Claim 40. While Craig discloses a method of cryopreservation that functions to store biomolecules of interest in

intact cells for extended periods this is only one element of the overall method of the presently claimed invention. As demonstrated above, Gonzales and Santoro are not properly combineable. However, even if, *arguendo*, these references are combined combined, a number of claim elements are not described or suggested. Therefore, Applicants respectfully request that this rejection be reconsidered and withdrawn.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider and withdraw all of the presently outstanding objections and rejections. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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